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Percentage of immature granulocytes in subacute thyroiditis follow-up and differential diagnosis with Graves' disease

Percentage of immature granulocytes in subacute thyroiditis and Graves' disease

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Abstract

Aim: Graves' disease (GD) and subacute thyroiditis (SAT) are common causes of thyrotoxicosis. Although the presence of neck pain is helpful in the differential diagnosis of these two entities some cases of SAT may have an atypical painless presentation. In recent years, the number of patients with painless SAT has been increasing in the literature and sometimes this may cause difficulties in differential diagnosis. Thus, auxiliary parameters other than clinical findings are needed for the correct diagnosis. In our study, we aimed to evaluate the immature granulocyte percentage (IG%), which is a new marker of acute inflammation, in the differential diagnosis of SAT, which is an inflammatory condition, and GD.

Material and Methods: In this study, data from 59 patients diagnosed with GD and 59 patients with SAT in the Endocrinology and Metabolic Diseases Outpatient Clinic of a tertiary medical care center, between January 2017 and October 2021 were retrospectively analyzed. Pre-treatment clinical and laboratory data obtained from patients who were diagnosed with SAT or GD were analyzed, IG% were recorded. The IG% were re-evaluated in patients after treatment.

Results: Pre-treatment IG% was found to be significantly higher in the SAT group when compared GD group. There was a significant decrease in IG% after treatment in SAT. In addition, steroid need was higher in patients with high IG% in the SAT group.

Discussion: Our study showed that IG% may be a helpful parameter in the differential diagnosis of GD and SAT and in predicting the need for steroids in SAT patients early.

Keywords
Immature Granulocyte Percentage, Subacute Thyroiditis, Graves' Disease

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Introduction

Thyrotoxicosis is the term used for excess thyroid hormone in the bloodstream. Hyperthyroidism is a condition in which excess thyroid hormone is synthesized and secreted from the thyroid gland. The most common causes of hyperthyroidism are Graves disease (GD) and toxic adenomas (TA) [1]. Subacute thyroiditis (SAT), silent thyroiditis, and postpartum thyroiditis are the causes of thyrotoxicosis, which occurs with the release of stored hormones into the blood due to the destruction of the follicles.

The differential diagnosis of thyrotoxicosis is important for treatment and follow-up. While SAT is a disease that can be resolved in a short time with nonsteroidal anti-inflammatory drugs (NSAIDs) -or steroids in patients who have severe symptoms that do not respond to NSAIDs, GD requires treatment with antithyroid agents and possibly thyroid surgery or radioactive iodine (RAI) treatment [2]. The differential diagnosis is based on clinical findings and hormonal and biochemical evaluation. The iodine uptake test can be used in differential diagnosis, but it is an expensive test and is not widely available. Additionally, the patient is exposed to radioactivity in the iodine uptake test and needs to be isolated for days after the test.

Immature granulocyte percentage (IG%) is a new inflammatory parameter [3]. Detection of immature granulocytes in peripheral blood, which is not seen in healthy people, is an indicator of bone marrow activation and acute inflammation [3,4]. Owing to the technological developments in automated hematological applications analyzers, IG% can be measured easily and quickly [5]. Recent studies have shown that IG% is a more effective predictor of the severity of infection than traditional markers such as white blood cell (WBC) count and C reactive protein (CRP) [4-7].

In this preliminary study, we aimed to evaluate the IG% in the differential diagnosis of SAT and GD and the utility of IG% in evaluating response to treatment in SAT. We also aimed to see if there is a parameter indicating the response to NSAIDs or the need for steroids in SAT patients.

Material and Methods

In this study, data from 59 patients diagnosed with GD and 59 patients with SAT in the Endocrinology and Metabolic Diseases Outpatient Clinic of a tertiary medical care center, between January 2017 and October 2021 were retrospectively analyzed. Ethics committee approval (No: E-21-787 / Date: 27.10.2021) was obtained.

The diagnosis of the GD was made in the presence of suppressed serum thyrotropin (TSH) level, high serum free T4 (fT4) and/or TSH receptor autoantibody (TRAB) level, which supports the presence of clinical hyperthyroidism with or without orbitopathy. In addition, diffuse hypoechoic appearance in thyroid ultrasonography and/or increased uptake of 99m-Tc pertechnetate in scintigraphy were confirmatory tests. The diagnosis of SAT was made with neck pain that started recently, the presence of tenderness in the thyroid region on physical examination, elevated erythrocyte sedimentation rate (ESR) and CRP levels accompanied by suppressed TSH and high free T4 and/or T3 values. Suppression in thyroid 99m-Tc pertechnetate uptake scintigraphy and heterogeneity in thyroid ultrasonography, hypoechogenicity compatible with decreased blood supply and thyroiditis areas, and pseudonodular appearance were confirmatory for the diagnosis.

Patients under the age of 18, pregnant women, patients with insufficient data, Graves' disease with subclinical hyperthyroidism or patients who prefer thyroid surgery or RAI treatment, patients with inflammatory, hematologic, immunological disease or patients receiving chemotherapy were not included in the study.

Pre-treatment clinical and laboratory data were obtained from patients who were diagnosed with SAT and who were scheduled to start antithyroid drug therapy due to Graves hyperthyroidism were examined, and variables included age, gender, initial serum TSH, serum TSH receptor antibody values, serum free T4 and T3 value, leukocyte counts, immature granulocyte percentages, ESR and CRP level were recorded. The patients were followed up after medical (methimazole/propylthiouracil for GD or non-steroidal anti-inflammatory agent or steroid for SAT) treatment. The IG%s were re-evaluated in patients with SAT, whose neck pain regressed and ESR, serum CRP and TSH levels were normalized, and in GD patients whose serum free T4 (FT4) and free T3 (FT3) levels returned to the normal range. Hematological analyzes of the patients were performed using the Sysmex XN 3000 instrument analyzer (Kobe, Japan). TSH, FT3, FT4 and TRAb were measured using the electrochemiluminescence method on a Roche Cobas 8000 analyzer (Rotkreuz, Switzerland).

Statistical analysis

SPSS 23 was used for statistical analysis. Normality was tested using the Shapiro–Wilk test. Data were presented as mean ± standard deviation (SD) for normally distributed variables, median (minimum–maximum) for non-normally distributed variables, and as the number of cases (%) for categorical variables. A chi-square test was performed for categorical variables to assess differences between groups. The comparisons between groups were performed by the Mann–Whitney U test for nonparametric variables considered to be associated with inflammatory parameters. Comparison of IG% levels of patients before and after treatment in both groups was done with the Wilcoxon test. P-values less than 0.05 were considered statistically significant.

Results

Demographic and biochemical data of the participants are shown in Table 1. Demographic parameters were similar between groups. IG% was found to be significantly higher in the SAT group compared to the GD group ($p<0,001$) at presentation. In the SAT group, 42% of patients had IG% >0.5. In the GD group, the IG% of all patients was <0.5. In the SAT group, post-treatment IG% was significantly lower than pre-treatment values ($p=0.001$). In the correlation analysis, a significant correlation was found between IG% and WBC ($r=0.401$, $p=0.02$) in the SAT group. There was also a strong positive correlation between IG% and steroid need ($r=0.328$, $p=0.011$). We did not find a correlation between IG% and CRP, ESR or the free t4 levels.

When SAT patients were grouped into two groups: IG%<0.5 and IG%>0.5, we found that more patients needed steroids for relief

Table 1. Demographic and laboratory data of the patients

	SAT	GD	p value
Age, years(min-max)	43(31-78)	41(18-74)	0.151
Sex (F/M)	43/16	46/13	0.521
WBC (10.9/L) (min-max)	8.7(5.5-16.2)	7.0(4.6-14)	0.001*
IG% (min-max)	0.52(0.1-1.9)	0.2(0.1-0.5)	<0.001*
TSH (mIU/L) (min-max)	0.01(0.01-0.7)	0.01(0.01-0.43)	0.001*
FT3 (ng/dL) (min-max)	6.1(2.48-19)	11.3(2.32-32.5)	<0.001*
FT4 (ng/dL) (min-max)	2.7(1.1-7.7)	3.3(1.1-7.7)	0.131
TRAb (min-max)	NA	11.7(1.7-408)	-
ESR (min-max)	44(3-106)	NA	-
CRP (mg/L) (min-max)	52(7.9-139)	NA	-

GD: Graves' disease, SAT: subacute thyroiditis WBC=White blood cells, IG=Immature granulocyte, TSH=thyroid-stimulating hormone, FT3=free triiodothyronine, FT4=free thyroxine, TRAb= thyroid stimulating hormone-receptor antibodies, ESR: erythrocyte sedimentation rate, CRP= C reactive protein. * significantly different, p<0.05

Table 2. Comparison of IG% with the development of hypothyroidism and need for steroids in SAT patients.

	Patients with IG%>0,5	Patients with IG%<0,5	p value
Hypothyroidism (n)	7/25(28%)	10/34(29%)	0.906
Need for steroids (n)	14/25(56%)	10/34(29%)	0.042*

IG%=Immature granulocyte ratio. * significantly different, p<0.05.

Table 3. Association between biochemical parameters and the need for steroids in patients with SAT.

	Steroid (+)	Steroid (-)	p value
WBC	9.6(7.1-15.5)	8.3(5.4-16.20)	0.027*
FT3	6.6(2.4-17)	5.49(2.4-19)	0.448
FT4	3.0(1.4-7.7)	2.7(1.1-7.7)	0.174
ESR	43(3.0-95)	46.5(20-106)	0.127
CRP	44.5(8.7-102)	57.9(7.9-139)	0.247
IG%	0.5(0.2-1.9)	0.4(0.1-0.9)	0.013*

WBC=White blood cells, FT3=free triiodothyronine, FT4=free thyroxine, ESR: erythrocyte sedimentation rate, CRP= C reactive protein, IG%=Immature granulocyte ratio.
* significantly different, p<0.05

of disease symptoms in the IG%>0.5 group when compared to the IG%<0.5 group in which most patients responded well to NSAIDs (p=0,042). The development of transient hypothyroidism was not different between these two subgroups of SAT (Table 2). When patients using and not using steroids were compared, WBC and IG% values were significantly higher in patients who needed steroids (Table 3).

Discussion

Our study showed that IG% was significantly higher in patients with SAT and may be helpful in the differential diagnosis of GD and SAT, in addition to other inflammatory parameters such as a high WBC count and CRP. High IG% at presentation may also predict unresponsive to NSAIDs in SAT patients and may guide the clinician to early management with steroids.

As an active bone marrow response in bacterial infections, a granulocytic shift to the left is seen with the presence of immature granulocytes in the peripheral blood [4,5]. Technical innovations have allowed automated hematology analyzers to identify and count IGs. This parameter has not been used sufficiently by clinicians yet. Recent studies have shown that the percentage and amount of granulocytes were significantly higher in many inflammatory conditions such as acute appendicitis, acute pancreatitis, sepsis and liver abscess [7,8-10].

In previous studies in healthy individuals, Saenz et al. found that the normal range of IG% in adults was<0.5% (sensitivity 82%) [11]. Lipiński et al suggested that IG% is a better and independent biomarker than WBC in the early diagnosis of severe acute pancreatitis (cut-off value of IG%>0.6, sensitivity of 100%, specificity of 96.2%) [12]. In our study, IG% was above>0.5% in 25 (42.3%) of 59 patients in the SAT group, and none of the patients in the Graves group had a value above 0.5%.

In a study by Karakulak et al. in patients with acute pancreatitis, higher IG% levels were found to be associated with higher disease severity and higher mortality in hospitalized patients [10]. In another study by Ünal et al in patients with necrotizing pancreatitis, it was shown that IG% had higher sensitivity and specificity than WBC, CRP and neutrophil lymphocyte ratio [7]. In this study, while the IG% value was 0.55 in the group discharged from the hospital, it was determined as 1.84 in the patients who died in the hospital. Park J.S. et al. reported that IG% had no additional benefit compared to other inflammatory markers for which the diagnostic ability for appendicitis was insufficient [13]. Güngör et al studied IG% in children with infection and found that IG% is more sensitive and specific in predicting the severity of bacterial infection when compared to other markers [14].

In recent years, changes have been observed in the clinical presentation of the SAT. In a study conducted in 2019, the frequency of painless SAT cases was determined as 6.25%, and recent studies reported that this rate increased during the pandemic period [15,16]. Despite advances in diagnostic tools, the differential diagnosis between thyrotoxicosis in GD and SAT may be difficult, particularly due to the lack of adequate access to all diagnostic tests, including in underdeveloped regions of the world. Some studies have analyzed the usefulness of simple blood count parameters in differential diagnosis. Platelet-to-lymphocyte ratio (PLR), monocyte-to-eosinophil ratio (Mo/Eo), neutrophil-to-lymphocyte ratio (NLR) are some of these, but the results are inconsistent [17-19].

SAT has a very high inflammatory load with very high ESR and CRP levels. In these patient groups, low cost and easy methods are needed. IG% is a new inflammatory marker and it is a quick, easy and inexpensive test. In our study, we found that IG% could be helpful in the differential diagnosis of patients with SAT and GD, and in predicting the response to NSAIDs or the need for steroids in the management of SAT. The limitation of our study is that it is a single-center, retrospective study with a relatively small number of patients.

Conclusion

This preliminary study showed that IG% is an inexpensive and widely available test that could be helpful in the differential diagnosis of patients with SAT and GD. IG% may also be helpful in predicting the response to NSAIDs or the need for steroids in the management of SAT. Early management of SAT patients with steroids may be considered in cases where IG% is high at presentation. Further studies with a higher number of patients may help clarify the role of IG% in the differential diagnosis of thyrotoxicosis and management of SAT.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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